STUDIES ON OMEGA OXIDATION OF FATTY ACIDS

BY

CARL FRANK AUGUST SIEVERT

B. S., Capital University, 1942

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
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R. UNIV. BIBLIOTHEEK LEIDEN

Introduction

Fatty acids can be oxidized in vivo, either on the beta or the omega carbon atoms. Beta oxidation, the main catabolic process was discovered by Knoop (1) in 1904. Omega oxidation was first discovered by Verkade (2) in 1933. Since that time there has been much speculation concerning the extent of omega oxidation. Verkade originally found that omega oxidation was limited to fatty acids with nine, ten and eleven carbon atoms. Since substitution of the fatty acid in the beta position blocks beta oxidation and decreases storage, thereby increasing omega oxidation, a series of β-phenyl fatty acids were prepared and administered to dogs, in order to determine the effect of chain length on omega oxidation.

Another highly debated topic is that of the precursor of the beta keto acid in the beta oxidation process. Several investigators have reported the presence of small amounts of β-methyl cinnamic acid in the distillate, after distilling the acid recovered from dog urine following the administration of β-phenylbutyric acid. These experiments were designed to use ultraviolet absorption spectra to detect the presence of α,β unsaturated acid in the urine following the administration of those β-phenyl fatty acids which are not omega oxidized.

Experimental

The β-phenyl fatty acids with chain lengths of from four to fifteen carbon atoms were synthesized by a method similar to that of Kohler (3) using benzalmalonic ester and the appropriate Grignard reagent, with subsequent saponification, acidification and decarboxylation of the product. During the distillation of the α-phenyltridecylmalonic ester, a small amount of a solid, unsoluble in hot concentrated sulfuric acid, was isolated. This substance was found to be tetracosane, formed by coupling of the lauryl magnesium

bromide. Small amounts of similar, insoluble materials were isolated from the esters formed from the longer chain Grignard reagents.

Since other methods of administration of the β-phenyl fatty acids had been only moderately successful, intraperitoneal injections of neutral isotonic solutions of the sodium salts of the β-phenyl fatty acids with chain lengths of four, five, seven and eight carbon atoms, were attempted. No difficulties were encountered upon injecting the β-phenylbutyrate or β-phenylvalerate salts. Injection of 100 ml. of solutions of the sodium salts of β-phenylheptanoic and β-phenyloctanoic acids were fatal to the dogs. Probably an increase in detergent qualities caused the hemorrhage noticed on autopsy.

The urine was acidified to pH 1 and extracted with ether. The ether extracts were passed over partition columns using ether as the mobile phase and phosphate buffers as the non-mobile phase. No separation of components, or of the acids from the colored impurities, was effected. One column, using cyclohexane as the mobile phase with 52 per cent methanol as the non-mobile phase, separated the acid from the colored impurities but did not give a quantitative recovery of the acid.

The ether extracts were then decolorized with carbon and the ether was distilled. The acid was dried *in vacuo*. The ultraviolet absorption spectra of the pure and the recovered acids were then obtained. The spectra of the pure acids were almost identical with the typical six point maximum of the benzene ring the dominant feature. The spectra of the recovered acids were similar to those of the pure acids but in each case there was more absorption in the region of 240 mμ. with a noticeable inflection point at 280 mμ.

The absorption spectrum of pure ethyl β-methylcinnamate showed a maximum at 240mμ. with a major inflection point

at 280 mμ.

The acid recovered by Hutchings (4) from dog urine following the administration of β-phenylhexanoic acid, which was similar to the above recovered acids in absorption of ultraviolet light, was then hydrogenated. The spectrum of the resulting compound showed less absorption at 240 and 280 mμ. with the reappearance of the sixth benzene ring peak at 242 mμ., which had been obscured by the increased absorption in that area. This indicates that the impurity in the recovered acid is the α,β unsaturated acid and provides strong evidence for the ability of the dog to desaturate fatty acids in the α,β position.

No evidence for the presence of omega oxidation products was found in the urine after the administration of the acids with less than nine carbon atoms in the chain.

The β-phenyl fatty acids with chain lengths of from ten to thirteen carbon atoms were administered orally in gelatin capsules encased in hamburger. Diarrhea ensued, with a resultant fecal contamination of the urine, but the dogs survived.

Partition columns using ether as the solvent and phosphate buffers as the non-mobile phase were used unsuccessfully in an attempt to separate the metabolic products. The ether extracts were then treated as in the previous experiments and the products fractionated with various solvents.

β-Phenyladipic acid was isolated from the urine after feeding β-phenyldecanoic and β-phenyldodecanoic acids. Less than ten per cent of the administered acid was recovered as β-phenyladipic acid.

No homogeneous compound was isolated after the administration of β-phenyltridecanoic and β-phenylpentadecanoic acids. Since no unchanged acid was recovered following the administration of any of the β-phenyl acids with ten or more carbon atoms in the chain, it is probable that the isolated

materials consisted of mixtures of omega oxidation products. The solubilities of the recovered material support this hypothesis.

Summary

The β-phenyl fatty acids with chain lengths of four, five, seven and eight carbon atoms were administered to a group of dogs and were excreted with about two per cent of the corresponding α,β unsaturated acid.

The β-phenyl fatty acids with chain lengths of from ten to thirteen carbon atoms were completely omega oxidized by the dog. Phenyladipic acid was isolated from the urine after feeding phenyldecanoic and β-phenyldodecanoic acids.

BIBLIOGRAPHY

1. Knoop, F. Beitr. Z. Chem. Phys. U. Path., **6,** 150 (1904).
2. Verkade, P. E., Elzas, M., van der Lee, J., de Wolff, H. H., Verkade-Sandbergen, A., and van der Sande, D., Z. Physiol. Chem. **215,** 225 (1933).
3. Kohler, E. P., Am. Chem. J., **34,** 146 (1905).
4. Hutchings, V. Z., Thesis, Bachelor of Science, University of Illinois (1947).

VITA

The author was born on October 25, 1920, in Blue Island, Illinois. He attended parochial grammar school and Community High School in that city. In 1938 he enrolled at Capital Univresity, receiving the Bachelor of Science degree from that institution in June, 1942. At that time he entered the graduate school of the University of Illinois, serving as Teaching Assistant in Chemistry from September, 1942, until February, 1944, and as Special Research Assistant in Chemistry from February until June, 1944. He was then inducted into the U. S. Naval Reserve, serving in the American Area until March, 1946, when he received an honorable discharge and reentered the University of Illinois. He held appointments as Teaching Assistant in Chemistry from June, 1946, until August, 1947.

He is a member of Sigma Xi, Phi Lambda Upsilon, and Alpha Chi Sigma.

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